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TITLE: Transgenic non-human animals capable of producing heterologous antibodies of various isotypes

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INVENTOR-INFORMATION:

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CLAIMS:

What is claimed is:

1. A transgenic mouse comprising an inactivated endogenous mouse immunoglobulin gene locus, said transgenic mouse further containing in its genome a transgene comprising in operable linkage a plurality of human V genes, a plurality of human D genes, a plurality of human J genes, a human .mu. C.sub.H gene, at least two different non-.mu. human C.sub.H genes and associated isotype switching sequences, wherein human .mu. and human .gamma. switch sequences are located in closer proximity to each other than in the naturally occurring human immunoglobulin locus; and wherein in lymphocytes of said mouse the transgene undergoes productive VDJ rearrangement and .mu. to .gamma. isotype switching by recombination between the human .mu. and human .gamma. switch sequences such that the mouse produces a serum containing immunoglobuline of at least three human heavy chain isotypes in detectable amounts in response to antigenic stimulation.

2. A transgenic mouse of claim 1, wherein the lymphocytes further have integrated a human light chain transgene.

3. A transgenic mouse of claim 2, wherein the serum comprises a population of IgG comprising a subpopulation of IgG composed of human .gamma.1 and human .kappa. and a subpopulation of IgG composed of human .gamma.3 and human .kappa..

4. The transgenic mouse of claim 3, wherein the inactivated gene locus is a mouse heavy chain immunoglobulin gene locus.

5. A mouse of claim 4, wherein the inactivated endogenous mouse

immunoglobulin heavy chain gene locus has intact V.sub.H and C.sub.H genes and lacks functional J.sub.H genes.

6. A mouse of claim 5, wherein said inactivated endogenous mouse immunoglobulin heavy chain locus further comprises a neo.sup.R gene replacing said J.sub.H genes between the endogenous V.sub.H genes and the endogenous C.sub.H genes of said heavy chain locus.

7. A mouse of claim 6, wherein the inactivated endogenous immunoglobulin heavy chain gene locus is a product of homologous recombination between J.sub.H KO1 and a mouse heavy chain allele of an ES cell of the AB-1 cell line.

8. A transgenic mouse having a germline genome with:

a human heavy chain transgene comprising in operable linkage a plurality of human V genes, a plurality of human D genes, a plurality of human J genes, a human .mu. C.sub.H gene, at least two different non-.mu. human C.sub.H genes and associated isotype switching sequences, wherein human .mu. and human .gamma. switch sequences are located in closer proximity to each other than in the naturally occurring human immunoglobulin locus; and wherein in lymphocytes of said mouse the transgene undergoes productive VDJ rearrangement and .mu. to .gamma. isotype switching by recombination between the human .mu. and human .gamma. switch sequences such that the mouse produces a serum containing immunoglobulins of at least three human heavy chain isotypes in detectable amounts in response to antigenic stimulation;

a human kappa chain transgene with a human V.sub..kappa. gene segment, human J.sub..kappa. gene segments, a human J-C.kappa. intronic enhancer, and a human C.sub..kappa. coding exon;

a pair of endogenous mouse heavy chain immunoglobulin loci, each of said loci having an inactivated heavy chain gene; and

a pair of endogenous mouse immunoglobulin kappa loci, each of said loci having an inactivated chain gene.

9. A mouse of claim 8, wherein said mouse makes an immune response to an antigen, said immune response comprising an antiserum containing antibodies that specifically bind to the antigen and wherein said antibodies comprise a human .mu. or .gamma. chain and a human .kappa. chain.

10. A mouse of claim 8, wherein the inactivated .kappa. chain gene has a deletion spanning J.kappa. and C.kappa..